

**FDA Psychopharmacological
Drugs Advisory Committee
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**Addendum to Briefing Document for
ZYPREXA[®] IntraMuscular
(olanzapine for injection)**

Eli Lilly and Company

**Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285**

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**Review of Data Pertinent to Bradycardia for the
ZYPREXA[®] IntraMuscular (olanzapine for injection)
Database**

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1. Executive Summary

Of the 850 total olanzapine-treated individuals in the IM olanzapine clinical trials in normal volunteers, non-agitated patients, and agitated patients, 64 individuals experienced bradycardia. Twenty-eight (43.8%) of the 64 were normal volunteers (representing 32.9% of normal volunteers). These cases of bradycardia included 3 cases (3 of 64 [4.7%]), all in normal volunteers (2 with IM and 1 with oral administration), of sinus pauses (lasting up to 6 seconds) that remitted spontaneously. Only 4.6% of agitated patients experienced sinus bradycardia with olanzapine and there were no cases of sinus pause in agitated patients. Forty (62.5%) of the 64 cases of bradycardia were associated with a decrement in resting blood pressure or an orthostatic drop. Therefore, the substantial majority of cases are consistent with a type of vasovagal bradycardia/syncope, referred to as neurally mediated reflex bradycardia (NMRB), as an etiology. Approximately 5 to 10% of the general population will display this reflex response to decreased venous return or to a decrement in blood pressure and it is a benign and self-limited phenomenon. The decrements in blood pressure and decreased venous return eliciting this reflex response in pre-disposed patients was likely facilitated by the α_1 antagonism of olanzapine.

With respect to adverse events that might be related to bradycardia in the controlled clinical trials, only 1 case of syncope occurred with olanzapine in either the placebo-controlled or haloperidol-controlled databases. Comparisons within these 2 databases did not suggest any significant excess of possibly hemodynamically-related adverse events among olanzapine-treated patients.

When comparing categorical changes in vital signs, the placebo comparison data indicate that olanzapine was associated with a greater incidence of resting hypotension (diastolic more so than systolic) as well as standing diastolic and systolic hypotension. Decrements in both supine and standing systolic pressure were such that the comparative incidence of orthostatic hypotension did not reach statistical significance. The relative difference in the comparative incidences of hypotension was greater than the relative difference in the comparative incidences of resting bradycardia. There was a 3.6% incidence of resting bradycardia with olanzapine and a 1.3% incidence with placebo (olanzapine 10 mg versus placebo database) and this comparison did not reach statistical significance ($p=0.229$). In comparison with haloperidol, differences were observed with respect to resting diastolic hypotension and standing systolic hypotension.

The intravenous animal data were quite consistent with the human data. Decrements in blood pressure were observed in rats given bolus injections (not infusion), cats given infusions (treated only by infusion), and dogs given bolus injections (not infusion). Decrements in heart rate were also observed in rats given bolus injection and dogs given bolus injection, but not the cats who experienced decrements in blood pressure when given infusions. In the rats and dogs given bolus injection, decrements in blood pressure without decrements in heart rate were observed at doses lower than the doses that produced decrements in both parameters. Also, the

decrements in blood pressure associated with decrements in heart rate were of greater magnitude than the decrements in blood pressure not associated with decrements in heart rate.

In summary, the total data support the position that IM olanzapine, probably due to its α_1 antagonism, can be associated with NMRB. This phenomenon is seen more frequently in normal volunteers (not agitated, not having a history of treatment with medications blocking multiple pressor transmitter receptors, and generally being young males probably with high vagal tone) compared to patients, more frequently seen in non-agitated patients compared to agitated patients, and more frequently seen in patients who have not recently taken antipsychotic medication compared to those who have been taking antipsychotic medication on a routine basis. In normal volunteers, slowing was observed to progress to brief periods of sinus pauses in 3 individuals. Telemetry ECG strips for these individuals reveal a pattern of sinus arrhythmia and bradycardia surrounding discrete, self-limited periods of pauses in sinus activity of up to 5 to 6 seconds duration. In all 3 individuals there was spontaneous resumption of sinus rhythm. Sinus pauses were not observed in clinical trial patients. This phenomenon of NMRB is viewed as a benign and self-limited reflex and this reflex may be elicited by venous pooling or hypotension in approximately 5 to 10% of the general population.

Conversely, the data presented above, in addition to supporting the hypothesis that olanzapine can be associated with NMRB, do not support the hypothesis that olanzapine has any direct effect on the sinus node leading to reduced automaticity of cardiac electrical activity. In intravenous infusion (up to 60 mg/kg over 1 hour - equivalent to 4,200 mg for a 70 kg human) and bolus (up to 20 mg/kg - equivalent to 1400 mg for a 70 kg human) studies in animals, some decrements in blood pressure were observed at the higher doses studied. Some decrements in blood pressure and heart rate were observed but only at higher doses than the doses associated with hypotension alone. If sinus node dysfunction was occurring, marked bradycardia would be expected rather than the moderate decrements in heart rate that occurred only in association with decreases in blood pressure. Additionally, in short- and long-term toxicology studies, mild increases in heart rate were observed, not decrement in heart rate, bradycardia, or asystole. The cases of self-limited sinus pulses in normal volunteers occurred surrounded by sinus arrhythmia and sinus bradycardia. This is in contrast to sustained periods of lack of sinus activity, with occasional sinus complexes and/or junctional and/or ventricular escape complexes that would be expected if olanzapine was adversely impacting sinus automaticity. Furthermore, the cases of self-limited sinus pauses in normal volunteers were observed in relatively young healthy individuals. The differences between olanzapine- and placebo-treated patients with respect to incidence of bradycardia were greater among younger patients (schizophrenia and bipolar studies) than among elderly patients (dementia study). This is consistent with NMRB where increased vagal tone (more common in younger than elderly individuals) facilitates NMRB as opposed to an adverse effect on the automaticity of the sinus node that would be facilitated and exacerbated by intrinsic sinus node disease (more common in elderly individuals than in younger individuals). In conclusion, all data are consistent with NMRB, and not a primary adverse effect on sinus node automaticity, as the etiology of bradycardia and the 3 cases of self-limited sinus pauses in normal volunteers. This is especially the case with respect to the actual recorded cardiac rhythms in the 3 individuals with pauses.

These rhythm strips are not consistent with or indicative of primary sinus node dysfunction. The observed transient sinus pauses in the 3 normal individuals represent the expression of a benign physiologic reflex, simply managed with patient observation, and not a life-threatening cardiac bradyarrhythmia or arrest.

2. Introduction

Of the 850 total olanzapine-treated individuals in the IM olanzapine clinical trials in normal volunteers, non-agitated patients, and agitated patients, 64 individuals experienced bradycardia. Twenty-eight (43.8%) of the 64 were normal volunteers (representing 32.9% of normal volunteers). These cases of bradycardia included 3 cases, all in normal volunteers (2 with IM and 1 with oral administration), of sinus pauses that remitted spontaneously. Only 4.6% of agitated patients experienced bradycardia and there were no cases of pause in electrical cardiac activity.

In order to most accurately assess the risk:benefit ratio of IM olanzapine, with respect to the effects of olanzapine on heart rate, a variety of data are pertinent. It is important to first define and identify these effects on heart rate. The physiology or mechanisms leading to these effects can then be understood as well as any special circumstances under which these effects might be observed. The clinical magnitude and incidence of these effects can then be compared with the magnitude and incidence observed with placebo or haloperidol or lorazepam when the active drugs have been administered as clinically intended in the target clinical populations. Additionally, data from animals treated with intravenous olanzapine are pertinent to the question of an actual effect or lack thereof.

3. Individual Human Data

3.1. Database and Methods

In order to be comprehensive in this review of human data, the heart rate and hemodynamic effects data presented are for the database comprised of all volunteers (n= 85), non-agitated patients (n=43), and agitated patients (n=722) exposed to at least one dose of olanzapine, referred to as the olanzapine patient and volunteer database. Although this is the database for the intramuscular formulation of olanzapine, in some cases (n= 2 of 85) the normal volunteers received *ONLY* oral olanzapine. There were 53 of the 85 normal volunteers who received both oral and IM olanzapine and the remaining 30 normal volunteers received only IM olanzapine. There were 755 patients (non-agitated, agitated) who received IM doses ≤ 10 mg and 10 agitated patients who received IM doses of 12.5 mg (total 765 patients). A total of 850 olanzapine-treated volunteers and patients are included in this database. This database includes 11 clinical studies.

A decrease in resting or positionally stressed (standing) heart rate of sufficient magnitude and/or absolute value to be considered to result in clinical bradycardia has been identified as the effect on heart rate of interest for this review. This is a result of 3 normal volunteers in Phase I studies experiencing pauses of cardiac electrical activity (sinus arrest versus SA block) of between 5 and 6 seconds (length not specified in 1 of the 3 subjects) that remitted spontaneously. Of note, there were no such cases among the 765 patients (non-agitated or agitated) receiving IM olanzapine.

Understanding of bradycardia and its possible etiologic mechanisms is best begun with identification and review of individual cases. In order to identify cases of pertinent decrements in heart rate, the following numeric vital signs data and ECG data were adopted as identifying criteria (Table 1).

Table 1. Descriptive Vital Sign and ECG Data Identifying Bradycardia

Vital Sign / ECG Finding	Criteria
Supine Pulse Low or Standing Pulse Low	Pulse rate < 50 and decrease from baseline of ≥ 15 (bpm)
ECG Heart Rate Low ^a	ECG heart rate ≤ 40 bpm

a Including telemetry for some normal volunteers.

These are the same numeric criteria that have been used to identify cases referred to as “potentially clinically significant” instances of change for the purpose of categorical analyses in previous olanzapine study reports and regulatory submissions. In addition to the numeric criteria based on vital signs and/or ECG data described above, a review of adverse events was

conducted to identify subjects or patients who had the adverse event term of bradycardia, pause, arrest, asystole, or syncope (any COSTART Term including the word “bradycardia,” “pause,” “arrest,” “asystole,” or “syncope” within the term).

3.2. Bradycardia

A search of the database revealed 28 normal volunteers (32.9% of normal volunteers; 43.8% of individuals experiencing bradycardia; [2 on oral of 2 receiving only oral; 7 on oral of 53 receiving oral and IM {3 of these 7 also on IM}; 10 on IM only of the 53 receiving oral and IM; 9 on IM of 30 receiving IM only]), 3 non-agitated patients (7% of non-agitated patients; 4.7% of individuals experiencing bradycardia); and 33 agitated patients (4.6% of agitated patients; 51.6% of individuals experiencing bradycardia) met criteria for experiencing treatment-emergent bradycardia. Thus, there were a total of 64 (7.5%) individuals who experienced bradycardia during treatment with oral and/or IM olanzapine from among 850 total olanzapine-treated individuals. These individuals are briefly summarized in Tables 16 to 18 in Appendix A. These tables summarize only individuals who received olanzapine and experienced bradycardia. The tables do not include normal volunteers who experienced bradycardia with placebo treatment or clinical trial patients who experienced bradycardia while receiving placebo, haloperidol, or lorazepam. Clinical comparator data will be presented subsequently.

One patient was identified in study LOAT (Patient LOAT 210) who met criteria for inclusion and is included in Table 16 in this review based on recent recognition that vital signs were described for the patient in the comments section of the patient’s clinical report form (CRF) that had not been recorded in the vital signs section of the patient’s CRF. Therefore, these vital signs had not been available to the electronic search for patients meeting numeric criteria.

3.3. Bradycardia with Hypotension or Orthostatic Hypotension or Failure of Appropriate Heart Rate Adaptation to Positional Change

In order to systematically review these cases it was considered appropriate to next identify the subset of individuals with resting (supine) bradycardia and 1) resting hypotension; or 2) orthostatic hypotension; or 3) failure of heart rate to show appropriate adaptation to positional challenge (standing). This search captured all 3 normal volunteers with pauses in cardiac electrical activity. Such individuals would be those most likely to be symptomatic and/or experience medical complications of bradycardia. The criteria for identifying such individuals are shown in Table 2 below.

Table 2. Descriptive Vital Sign and ECG Data Combinations

Combination of Potentially Clinically Significant Vital Signs	Criteria
Bradycardia with Hypotension	
Supine Pulse Low and Supine Systolic Blood Pressure Low	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and supine systolic blood pressure ≤ 90 and decrease from baseline of ≥ 20 (mmHg)
Supine Pulse Low and Supine Diastolic Blood Pressure Low	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and supine diastolic blood pressure ≤ 50 and decrease from baseline of ≥ 15 (mmHg)
ECG Heart Rate Low and Supine Systolic Blood Pressure Low	ECG heart rate ≤ 40 bpm and supine systolic blood pressure ≤ 90 and decrease from baseline of ≥ 20 (mmHg)
ECG Heart Rate Low and Supine Diastolic Blood Pressure Low	ECG heart rate ≤ 40 bpm and blood pressure ≤ 50 and decrease from baseline of ≥ 15 (mmHg)
Bradycardia with Orthostatic Hypotension	
Supine Pulse Low and Orthostatic Systolic Blood Pressure Drop	Supine pulse rate <50 and decrease from baseline of ≥ 15 (bpm) and ≥ 30 mmHg decrease in systolic BP (supine to standing)
ECG Heart Rate Low and Orthostatic Systolic Blood Pressure Drop	ECG heart rate ≤ 40 bpm and ≥ 30 mmHg decrease in systolic BP (supine to standing)
Bradycardia with Failure of Appropriate Heart Rate on Adaptation on Positional Challenge	
Supine Pulse Low and Standing Pulse Low	Supine and standing pulse rate <50 and decrease from baseline of ≥ 15 (bpm)
ECG Heart Rate Low and Standing Pulse Low	ECG heart rate ≤ 40 bpm and standing pulse rate <50 and decrease from baseline of ≥ 15 (bpm)

In addition to the numeric criteria based on vital signs and/or ECG data described, a review of adverse events, combined with vital sign and ECG data, was conducted to identify subjects or patients who had a potentially clinically significant low pulse rate or ECG heart rate or the adverse event term of bradycardia/pause/arrest/asystole in combination with an adverse event related to hypotension (e.g., hypotension, postural hypotension, dizziness, syncope). This additional review was conducted to capture subjects or patients who may not have been able to stand (i.e., standing vital signs not available) but who also had evidence of bradycardia associated with hypotension.

In total, 15 (23.4%) of the 64 total individuals experiencing bradycardia did so in the context of hypotension, orthostatic hypotension, or failure of appropriate heart rate adaptation on

positional change. Individual case reviews of all 15 cases are displayed in summary fashion in Table 3 below. This table summarizes only individuals who received olanzapine and experienced bradycardia. The table does not include normal volunteers who experienced bradycardia with placebo treatment or clinical trial patients who experienced bradycardia while receiving placebo, haloperidol, or lorazepam. Clinical comparator data will be presented subsequently.

The summary in Table 3 below makes obvious pertinent facts in these cases (e.g., a majority of the cases were normal volunteers).

3.3.1. *Tabular Summary of Individual Cases*

Table 3. Summary of Abnormalities in Individuals with Bradycardia and Hypotension, Orthostatic Hypotension, or Failure of Appropriate Heart Rate Adaptation on Positional Challenge

Study Type Subject/ Patient	Abnormalities Present After Study Drug Administration						Baseline Drug Status		Abnormalities Present at Baseline				
	Resting BP↓ >10 ^a	Resting Pulse ↓ >10 ^b	Ortho BP ↓ >10 ^c	Failure of Ortho Pulse↑ ^d	Cardiac Electrical Pause	Symptoms	Anti- psychtc e	α-1 antagonst ^f	Ortho Pulse↑ ≥10 ^g	Ortho Pulse↓ ≥10 ^h	Ortho BP ↓ ≥15 ⁱ	Pulse <60 ^j	ECG Abn ^k
Normal Volunteer													
LOAC 32 (oral only)	+	-	+	-	+	Nausea Hypotension Dizziness Syncope after voiding Headache Tremor	-	-	-	-	+	+	-
LOAC 33 (oral only)	+	+	+	-	-	Somnolence Headache	-	-	+	-	-	-	-
LOAV 2766	+	+	na	na	-	Somnolence	-	-	-	+	+	+	-
LOAV 2843	+	+	na	na	nc	Somnolence Syncope on standing to void ↓ Respiration (4- 7/min) Bradycardia Incontinence (U and B) Hypertonia Tremor Malaise Pallor	-	-	+	-	-	+	-
LOAW 2	+	+	+	+	+		-	-	+	-	-	+	LAD
LOAW 15	+	+	+	-	+	Nausea Hypotension Dizziness	-	-	+	-	-	-	LAH
HGIO 9	+	-	+	-	nc	Somnolence	-	-	+	-	-	+	-

Table 3. (Concluded) Summary of Abnormalities in Individuals with Bradycardia and Hypotension, Orthostatic Hypotension, or Failure of Appropriate Heart Rate Adaptation on Positional Challenge

Study Type Patient/ Subject	Abnormalities Present After Study Drug Administration						Baseline Drug Status		Abnormalities Present at Baseline				
	Resting BP↓ >10 ^a	Resting Pulse ↓ >10 ^b	Ortho BP ↓ >10 ^c	Failure of Ortho Pulse↑ ^d	Cardiac Electrical Pause	Symptoms	Anti- psychotc _e	α-1 antagonst ^f	Ortho Pulse↑ ≥10 ^g	Ortho Pulse↓ ≥10 ^h	Ortho BP ↓ ≥15 ⁱ	Pulse <60 ^j	ECG Abn ^k
Non-agitated Psychotic No control													
HGJA 1013	+	+	+	-	nc	Dizziness Bradycardia Postural hypotension Somnolence	-	-	+	-	+	-	SB
Agit.,Psychoti c, No Control													
LOAT 162	+	+	+	-	nc	Dizziness Syncope	-	-	+	-	-	+	SB
LOAT 163	+	+	+ ^m	-	nc	Dizziness	Flu	-	+	-	-	-	-
LOAT 164	+	+	+	-	nc	Dizziness Headache	-	-	+	-	-	+	-
LOAT 210	+	+	-	na	nc	Agitation Insomnia Nervousness	-	-	+	-	-	-	-
Agit.,Psychoti c Controlled													
HGHB 6103 ¹	+	-	+	-	nc	Bradycardia Dizziness Headache	Risp	Risp	+	-	+	-	SB
HGHV 9090	+	+	+	-	nc	Dizziness Hypotension	-	-	+	-	-	+	SB
HGHV 9351 ¹	+	-	+	-	nc	Hypotension	Hal	-	+	-	-	+	SA, ERp

Footnotes on next page
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Olanzapine for Injection

- a Change from latest baseline value in supine systolic blood pressure of >10 mmHg.
- b Change from latest baseline value in supine pulse of >10 bpm.
- c Decrease in systolic blood pressure from supine to standing of >10 mmHg.
- d No increase in pulse of ≥ 10 bpm from supine to standing, to compensate for decrease in blood pressure of >10 mmHg
- e Patient received an antipsychotic within 2 days of first injection and had been receiving it for at least 5 consecutive days.
- f Patient received a medication with significant alpha-1 antagonism within 2 days of first injection and for at least 5 consecutive days prior to that.
- g Increase in pulse from supine to standing of ≥ 10 bpm at any baseline assessment.
- h Decrease in pulse from supine to standing of ≥ 10 bpm at any baseline assessment.
- i Decrease in systolic blood pressure from supine to standing of ≥ 15 mmHg at any baseline assessment.
- j Pulse <60 bpm at any baseline assessment.
- k ECG abnormality at baseline
- l Patient met criteria for inclusion and review, but review of detailed case material indicated that decrease in heart rate did not actually accompany decrease in blood pressure. (See text for greater detail.)
- m The decrease did not occur after the 1st injection when the dizziness was reported. This decrease occurred after the 2nd injection which was administered on the following day; no dizziness was reported after the 2nd injection.

Abbreviations: ERp = early repolarization, Flu = fluphenazine decanoate, Hal = haloperidol, U and B = urinary and bowel, LAD = left axis deviation, LAH = left anterior hemiblock, na=not assessed, nc=no continuous cardiac monitoring, Risp = risperidone, SB = sinus bradycardia, SA = sinus arrhythmia

3.3.2. Discussion of Individual Cases Suggesting Etiological Mechanism of Bradycardia

Careful review of these cases brings several important clinical facts to light regarding individual cases. First, 2 of these 15 cases, (Patient HGHB 6103 and Patient GHV 9351), although meeting formal criteria for inclusion in this review, and having a decrement in resting blood pressure and experiencing some degree of orthostatic hypotension, the “bradycardia” resulting in their inclusion occurred independently of hypotensive/orthostatic hypotensive findings. Although this fact was implicit in the detailed text of the case reviews included in the original submission, it was not emphasized in summary fashion or discussed in detail.

Patient HGHB 6103 was included because he had the adverse events of “bradycardia” and “dizziness” recorded, along with having objective orthostatic hypotension (decrease of 20 mmHg systolic blood pressure on standing) at 2 hours following injection, but his resting pulse of 56 bpm was down only 4 bpm from baseline. Furthermore, his standing pulse was 84 bpm. He did not actually have clinical treatment-emergent bradycardia or any decrement in heart rate on orthostatic challenge.

Patient GHV 9351 was included because he had an adverse event recorded as “hypotension” that did not resolve until 24 hours following the dose at which time the standing pulse was 47 bpm. The patient never had objective, treatment-emergent resting bradycardia (supine pulse: 49 bpm at 2 hours, 57 bpm at 24 hours, baseline 53 bpm) and at the time of recording the standing pulse of 47 bpm (24 hours), his blood pressure was 109/68 mmHg. The decrease in heart rate of 10 bpm (57 bpm resting to 47 bpm on standing) at 24 hours was not associated with orthostatic hypotension (supine BP: 116/70 mmHg, standing BP: 109/68 mmHg) so this decrease was not a failure of pulse adaptation to an orthostatic decrement in blood pressure.

Neither of these patients actually represented cases of clinical bradycardia associated with hypotension or orthostatic hypotension that was treatment-emergent. Both patients simply had mild orthostatic hypotension.

Secondly, the case of Subject LOAV 2843 appears clinically quite serious because cardiopulmonary resuscitation was initiated on this subject following a syncopal episode and one of the adverse events observed immediately following the syncopal episode was described with the COSTART classification term “APNEA.” However, his lowest documented pulse rate was 33 bpm at the time of resuscitation and an infusion of atropine was discontinued shortly after initiation (he received only 0.2 mg) because the pulse rate rose spontaneously. According to the documentation of vital signs at the time of resuscitation efforts, the respiratory rate was 4 to 7/min (down from a baseline of 16/min) and this does not constitute apnea but rather respiratory depression. This clinical interpretation is substantiated by the documentation of pulse oximetry. O₂ saturation before the syncopal episode was 97% and decreased only 3% during this episode. The most specifically correct COSTART classification term for this event is “HYPOVENTILATION.” The detailed clinical facts of this case are actually more consistent with those of the other cases of hypotension and bradycardia rather than being of the

seriousness suggested by the use of the COSTART term “APNEA” and the initiation of a resuscitation effort.

Another aspect of these cases is that there were three subjects with ECG confirmed sinus pause (LOAC 32; LOAW 2; LOAW 15). Subject LOAC 32 was a 26-year-old male who had a degree of orthostatic hypotension at baseline (supine BP: 116/66 mmHg, HR: 59 bpm; standing BP: 99/52 mmHg, HR: 61 bpm) and who had an asymptomatic pause of 5 seconds duration associated with nausea occurring 2 hours following **oral** olanzapine 10 mg and a second 5 second pause at 4½ hours following the dose, just prior to standing and urinating. Severe dizziness and syncope followed urination. In both instances of pause the resolution of normal rhythm was spontaneous without treatment. Both pauses were preceded and followed by sinus arrhythmia and sinus bradycardia. Between episodes, the supine vital signs were BP 84/34 mmHg and HR 50 bpm.

Subject LOAW 2 was a 55-year-old male who had a 5 to 6 second pause, **while standing**, accompanied by syncope at 1 hour following IM olanzapine 5 mg and a second 5 to 6 second pause and syncope again **while standing** approximately 6 hours following the IM dose. Blood pressure and pulse were obtained immediately before the second episode in both the supine and standing positions. In the supine position they were 100/65 mmHg and 58 bpm. In the standing position they were 53/35 mmHg and 54 bpm. Both pauses resolved spontaneously without treatment. The pauses were associated with sinus arrhythmia and sinus bradycardia.

Subject LOAW 15 was a 47-year-old male with an upper respiratory infection and fever the evening prior to the study. He experienced an asymptomatic pause (duration not specified) at ¾ hours following a second IM olanzapine 5 mg dose (which followed a first injection by 4 hours). He developed cough, nausea, and dizziness following the first dose. He was quite sedated and had been lying down for ¼ hours at the time of the pause. At 2 minutes following the sinus pause his supine blood pressure and pulse were 71/41 mmHg and 45 bpm. One minute later these values were 76/42 mmHg and 42 bpm. The pause resolved spontaneously without treatment. The pause was associated with sinus arrhythmia and sinus bradycardia.

Therefore, 3 normal volunteers experienced 5 episodes of a pause in cardiac electrical activity. One volunteer experienced 2 episodes of pause following oral administration of olanzapine. Three of the 5 episodes of pause occurred on positional change to standing and other factors associated with various subtypes of vasovagal syncope including hypotension, orthostatic hypotension, micturation (urination), nausea, and dizziness.

It is possible that Subject LOAV 2843, the subject for whom resuscitation efforts were initiated, had a sinus pause in association with his syncopal episode that occurred while the subject was standing to urinate 1 hour after receiving IM olanzapine 5 mg. However, no pause was documented and the heart rate documented following syncope was 33 bpm. If this patient did suffer a pause, it resolved spontaneously.

On initial consideration, these sinus pauses might suggest a significant clinical risk. However, all 3 normal volunteers with documented pauses had spontaneous resolutions of these pauses and if a 4th normal volunteer had a pause it also resolved spontaneously.

In addition to the clinical facts of these cases, the likely mechanism leading to these pauses suggests that such pauses are benign and self-limited from a cardiac rhythm perspective. As will be discussed in more detail immediately below, all 15 cases reviewed (only 13 actual cases based on case detail) with hypotension and/or orthostatic hypotension accompanied by bradycardia (3 described above with bradycardia to the point of pause) are very consistent with a form of vasovagal syncope (Lazarus and Mauro 1996; Henderson and Prabhu 1997) previously referred to as neurocardiogenic bradycardia/syncope (Bezold-Jarisch Reflex) and now referred to as neurally mediated reflex bradycardia/syncope (NMRB). This physiologic process is generally considered benign, simply requiring recumbent posture for effective treatment, as described in *Harrison's: Principles of Internal Medicine* (Daroff and Martin 1998):

“The net result is a vicious cycle of *inappropriate peripheral vasodilation and relative bradycardia* leading to progressive hypotension and syncope **that can be reversed by assumption of supine posture and elevation of the legs.**” (bold emphasis added)

It has recently been recognized that a small proportion of patients experiencing NMRB will have pauses (Maloney et al. 1988; Milstein et al. 1989; Grubb and Kosinski 1996). It has also been recognized that this phenomenon of NMRB can be observed in individuals while they are supine (Van Lieshout et al. 1997).

Additionally, it is notable that all 15 of these cases involved some degree of decrement in resting blood pressure (systolic and/or diastolic blood pressure decreased ≥ 10 mmHg from baseline) and/or orthostatic drop (drop of ≥ 10 mmHg systolic pressure when moving from supine to standing position). This is in the context of identifying this subgroup of bradycardic patients not only with hypotension or orthostatic hypotension but potentially with only a failure of adequate heart rate adaptation on positional challenge. Therefore, all patients who were identified for inclusion in this subgroup based on failure of adequate heart rate adaptation on positional challenge also had some significant degree of decrement in blood pressure and/or orthostatic drop. This underscores the likelihood of NMRB as the etiology of these cases of bradycardia.

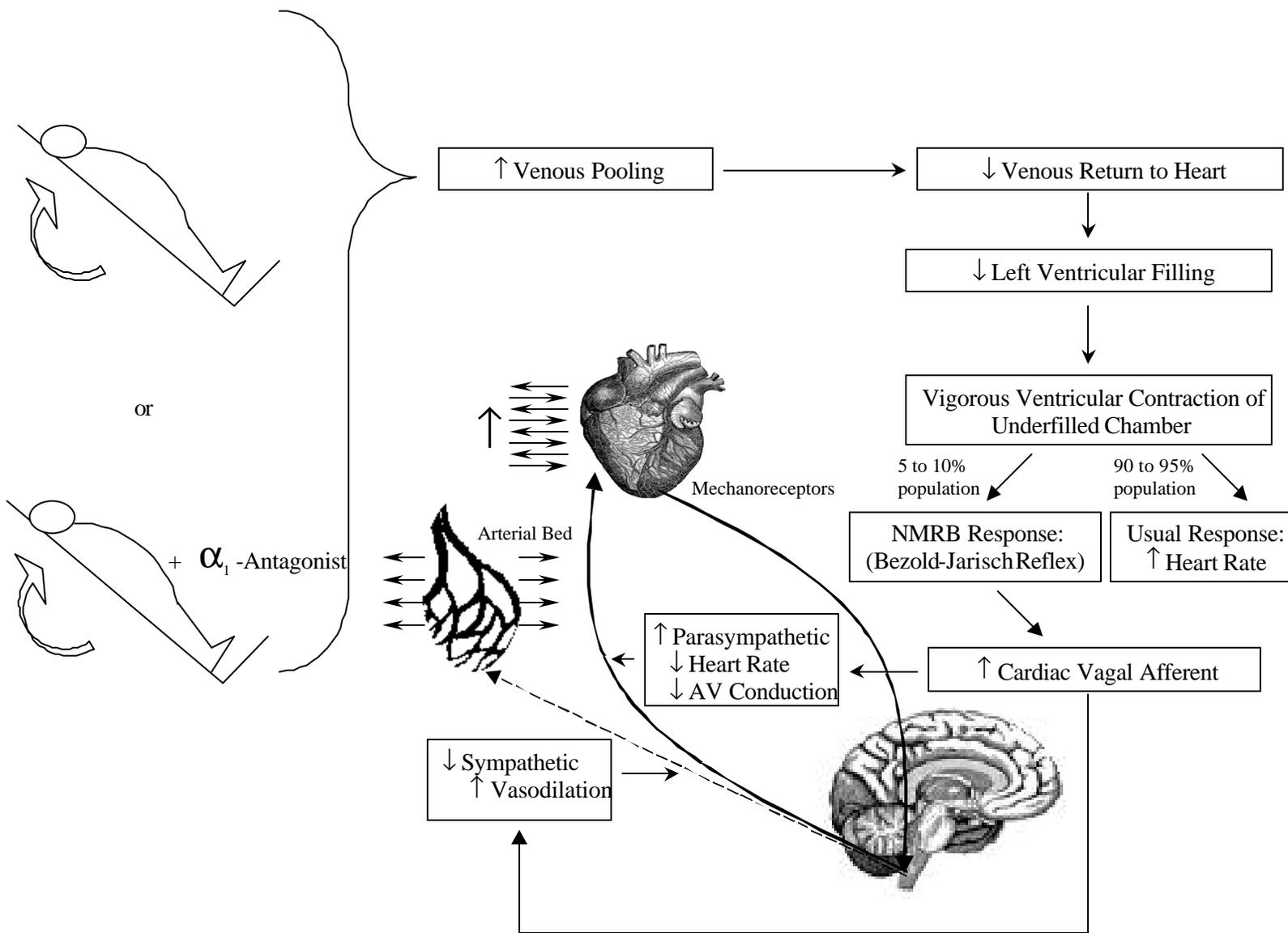
Finally, it is important to recognize two additional related aspects of these cases. First, 7 (53.8%) of these 13 actual cases were in normal volunteers (2 of these 7 receiving oral medication), all of whom were healthy and not on any chronic medications. It is well recognized that normal volunteers who are not agitated and have not had exposure to centrally acting neurotransmitter antagonists show a greater incidence of changes in autonomic activity and that their responses are not necessarily predictive of those in agitated patients (Sramek et al. 1997; Pokorny et al. 1994). An additional case occurred in a non-agitated patient with schizophrenia participating in study HGJA, a clinical pharmacology trial. IM olanzapine would not be used clinically in such a patient. Of the 5 actual agitated patient cases identified (LOAT 62, LOAT

163, LOAT 164, LOAT 210, HGHV 9090), only 1 (LOAT 163) had been recently treated with antipsychotics (fluphenazine) and none had been recently treated with any medication with any significant α_1 -antagonist properties. Fluphenazine has relatively little α_1 -antagonist activity.

This difference in the potential to experience decrements in blood pressure depending on recent medication treatment is underscored by results of study HGJA. In this study, at one investigative site only 1 of 23 non-agitated patients was receiving antipsychotic therapy at baseline, while at the other site 17 of 20 similar patients were receiving ongoing antipsychotic therapy at baseline. More decrements of greater magnitude in blood pressure occurred in patients acutely naive to antipsychotic medication compared to patients receiving continuing antipsychotic medication in this study.

3.3.3. *Probable Etiologic Mechanism of Bradycardia: Neurally Mediated Reflex Bradycardia (Bezold-Jarisch Reflex)*

As suggested above, these cases are consistent with the physiologic mechanism of NMRB. Some factor leading to a degree of venous pooling is necessary to initiate the NMRB cascade of events of venous pooling → increased cardiac contractility → bradycardia and decreased vascular tone. This factor with olanzapine is likely a combination of its α_1 -adrenergic receptor antagonism resulting in decreased peripheral vascular resistance and the sedation that frequently results in those who receive the medication assuming a supine posture for extended periods, facilitating venous pooling (see figure below).



A first dose effect leading to hypotensive symptoms, with rapid tachyphylaxis, has been described for 10 to 20 % of patients receiving α_1 -adrenergic antagonists such as prazosin (Carruthers 1994). Some of these patients may experience NMRB due to their hypotension. However, not all individuals who experience decrements in resting blood pressure or decrements in blood pressure on orthostatic challenge will respond with NMRB. The more common response to the decrease in blood pressure is the expected increase in heart rate to maintain systemic perfusion.

An important clinical implication of this likely mechanism of olanzapine influence on blood pressure and heart rate is the potential for both positive and negative pharmacodynamic drug interaction. It is unlikely that there would be an additive effect of olanzapine on other medications with substantial α_1 -adrenergic antagonist activity. In fact it would be probable that use of a medication with α_1 -adrenergic antagonist properties at the time of initiation of olanzapine would reduce the likelihood of hemodynamic alterations with olanzapine. Additive effects might be observed with medications reducing blood pressure or heart rate by mechanisms other than α_1 -antagonism. However, the situation is complex since medications with negative inotropic activity may interrupt this reflex loop by reducing the increased ventricular contractility believed important in NMRB. For example, beta blockers have been used as an effective treatment for NMRB (Lazarus and Mauro 1996).

It is notable that only 5 of 765 (0.65%) total patients experienced bradycardia with hypotension, orthostatic hypotension, or failure of appropriate heart rate adaptation to positional change, including 3 at doses in excess of those intended for clinical use. Therefore, only 2 of 755 (0.26%) patients treated within intended dosing recommendation actually experienced this phenomenon. As pointed out above (Table 3), both these patients were acutely naive to antipsychotics/ α_1 -adrenergic antagonist medications. However, a substantial percentage of the agitated patients treated in clinical trials were probably acutely naive to these medications. The likely reason that so few patients receiving olanzapine as clinically intended experienced NMRB is that agitation, itself, is associated with a peripheral catecholamine and neurohormonal status that increases heart rate and vascular tone (Harvey 1996). Further, agitation is independent of specific psychiatric diagnosis (Harvey 1996) such that an agitated patient, for example a patient with dementia, might be expected to be less likely to experience decrements in blood pressure and heart rate as is the agitated patient with schizophrenia, in comparison to the normal volunteer or patient without agitation (Sramek et al. 1997). It would appear from clinical data collected in these trials that the state of agitation is protective against the hemodynamic effects of α_1 -antagonism.

An understanding of NMRB from both physiological and epidemiological perspectives is helpful in assessing the risk:benefit ratio of IM olanzapine. Recent reviews (Kosinski et al. 1995; Kaufmann 1995; Morillo et al. 1997) provide detailed explanations of the current understanding of cardiac and neural processes involved that have been explained above. During venous pooling, a reduced pre-load state (resting hypotension, orthostatic hypotension), increased ventricular contractility occurs which results in increased efferent activity from ventricular mechanoreceptors. Rostral ventral lateral centers of the medulla respond to this increased

afferent activity by 1) increasing parasympathetic efferent activity to the heart resulting in a decrease in heart rate; and 2) decreasing sympathetic outflow, resulting in a further decrease in vascular resistance, that leads to further decrease in blood pressure. Data have suggested that in addition to withdrawal of sympathetic tone, alterations in neurohormonal activity is necessary to produce sufficient vasodilation to result in symptomatic NMRB (Kaufmann, 1995). Furthermore, increased afferent input from the ventricles may not be necessary to initiate NMRB (Kauffman 1995; Morillo et al. 1997).

NMRB is relatively common in the general population. Syncope has a lifetime prevalence of between 3.0% to 3.5% in the general population (Kaufmann 1995). A review by Linzer et al. (1997) suggests that 18% (range 8% to 37%) of cases of syncope are vasovagal without a specific activity precipitant (likely cases of NMRB), and that an additional 8% (range 4% to 12%) of cases of syncope occur in the context of orthostatic hypotension where mechanisms similar to those of NMRB might come into play. Therefore, based on Linzer's review, 26% and perhaps up to 49% of clinical cases of syncope represent NMRB. Kaufmann (1995) reported that 41% of cases of syncope have NMRB as the etiology. More importantly, even without a history of clinical syncope, a tilt table test (method of producing venous pooling and subsequent orthostatic hypotension) produces symptomatic NMRB in 5% to 10% of the general population (Fitzpatrick et al. 1991; Kaufmann 1995; Kapoor 1999).

There are two important implications of these epidemiological data for the risk:benefit ratio of IM olanzapine. First, the relatively common prevalence of NMRB to the point of syncope in the general population, up to 1.4% (perhaps 41% of 3.5% prevalence of syncope) underscores the relatively benign nature of the phenomenon with respect to cardiac electrophysiology and rhythm (indirect consequences of falls during syncope can certainly be serious). Second, the capacity to induce this phenomenon in up to 10% of normal individuals without a history of syncope underscores the potential for cases observed during IM olanzapine treatment to not be actually caused by olanzapine. Any antipsychotic or combined antipsychotic-sedative that quickly produces a desirable level of sedation might be associated with some cases of NMRB, not due to a direct pharmacologic effect on vascular resistance but secondary to the sedation that promotes venous pooling of blood.

3.4. Bradycardia with a Decrement in Blood Pressure

There were 49 remaining individuals from among the 64 who had been identified as having bradycardia during treatment with oral and/or IM olanzapine, but who had not met criteria for hypotension, orthostatic hypotension, or failure of adequate heart rate adaptation on positional challenge. The clinical data for these 49 were reviewed in order to determine if their bradycardia occurred in the context of some decrement in blood pressure or some orthostatic drop. If such were the case, their clinical course would be considered consistent with NMRB as the etiology of their bradycardia. Table 4 reflects the criteria used to determine if these individuals experienced their bradycardia in the context of a decrease in blood pressure or an orthostatic drop.

Table 4. Descriptive Vital Sign and ECG Data Identifying Bradycardia in the Context of Decrease in Blood Pressure or Orthostatic Drop

Basis for Bradycardia	Criteria for Decrement in Blood Pressure or Orthostatic Drop
Supine Pulse or ECG Heart Rate	Supine Systolic or Diastolic Pressure Decrease from Baseline ≥ 10 mmHg
Standing Pulse	Standing Systolic or Diastolic Pressure Decrease from Baseline ≥ 10 mmHg; or Orthostatic Drop ≥ 10 mmHg

Table 19 in Appendix A summarizes these individuals. This table summarizes only individuals who received olanzapine and experienced bradycardia. The table does not include normal volunteers who experienced bradycardia with placebo treatment or clinical trial patients who experienced bradycardia while receiving placebo, haloperidol, or lorazepam. Clinical comparator data will be presented subsequently.

The 25 (51.0%) individuals listed in Table 19 of the 49 remaining individuals, after accounting for those individuals who experienced their bradycardia in the context of hypotension, orthostatic hypotension, or failure of appropriate heart rate adaptation on positional challenge, experienced their bradycardia in a context of a decrement in blood pressure or an orthostatic drop. The etiology of their bradycardia can be considered consistent with NMRB. Of the 64 individuals with bradycardia, 62.5% had a clinical course that was considered consistent with NMRB. Only 24 (2.8%) of the 850 total individuals in the database experienced an event of bradycardia that was not clearly consistent with NMRB.

3.5. Bradycardia Without a Decrement in Blood Pressure

Table 20 in Appendix A summarizes the 24 individuals experiencing bradycardia where the bradycardia was not clearly consistent with an etiology of NMRB. This table summarizes only individuals who received olanzapine and experienced bradycardia. The table does not include normal volunteers who experienced bradycardia with placebo treatment or clinical trial patients who experienced bradycardia while receiving placebo, haloperidol, or lorazepam. Clinical comparator data will be presented subsequently.

Of these 24 individuals, 4 were normal volunteers who experienced bradycardia after oral olanzapine (1 also experiencing bradycardia following 2 injections of IM olanzapine). There were 5 normal volunteers and 15 patients who experienced their bradycardia following one or more IM injections. The data from individuals who experienced bradycardia and received a single injection are the most informative regarding the time course of this phenomenon. There were 9 individuals receiving a single injection. Four of these individuals experienced bradycardia within 3 hours of injection; 2 individuals between 3 and 6 hours of injection; and 3 individuals between 12 and 24 hours of injection.

3.6. Summary of Individual Human Data

Of the 850 total olanzapine-treated individuals in the IM olanzapine clinical trials in normal volunteers, non-agitated patients, and agitated patients, 64 individuals experienced bradycardia. Twenty-eight (43.8%) of the 64 were normal volunteers (representing 32.9% of normal volunteers). These cases of bradycardia included 3 cases (3 of 64 [4.7%]), all in normal volunteers (2 with IM and 1 with oral administration), of sinus pauses (lasting up to 6 seconds) that remitted spontaneously. Only 4.6% of agitated patients experienced sinus bradycardia with olanzapine and there were no cases of sinus pause in agitated patients. Forty (62.5%) of the 64 cases of bradycardia were associated with a decrement in resting blood pressure or an orthostatic drop. Therefore, the substantial majority of cases are consistent with a type of vasovagal bradycardia/syncope, referred to as neurally mediated reflex bradycardia (NMRB), as an etiology. Approximately 5 to 10% of the general population will display this reflex response to decreased venous return or to a decrement in blood pressure and it is a benign and self-limited phenomenon. The decrements in blood pressure and decreased venous return eliciting this reflex response in pre-disposed patients was likely facilitated by the α_1 antagonism of olanzapine.

4. Human Comparative Clinical Trial Data

4.1. Non-Quantitative Hemodynamic Adverse Event Comparative Data

Comparisons of non-quantitative hemodynamic adverse event profiles in the IM controlled clinical trials provide data pertinent to the clinical significance of bradycardia. Tables 5 and 6 below compare the incidences of clinically described non-quantitative hemodynamic adverse events for the placebo-controlled and haloperidol-controlled databases. All doses of olanzapine were pooled as the incidences of events for individual dose groups were extremely low. The placebo-controlled database provides data regarding causality with olanzapine and the haloperidol-controlled database provides comparison with standard therapy. Only 1 case of syncope occurred with olanzapine in these 2 databases. These 2 databases do not suggest any substantial excess of non-quantitative hemodynamically-related adverse events among olanzapine-treated patients.

Table 5. Treatment-Emergent Non-Quantitative Adverse Events Related to Bradycardia or Hypotension Placebo-Controlled Database

Event Classification	IM Olanzapine (N=415)		IM Placebo (N=150)		p-value
	n	%	n	%	
Dizziness	17	4.1%	3	2.0%	0.307
Syncope	1	0.2%	0	0%	1.00

Table 6. Treatment-Emergent Non-Quantitative Adverse Events Related to Bradycardia or Hypotension Haloperidol-Controlled Database

Event Classification	IM Olanzapine (N=316)		IM Haloperidol (N=166)		p-value
	n	%	n	%	
Dizziness	8	2.5%	3	1.8%	0.755
Syncope	0	0%	0	0%	--

4.2. Categorical Vital Sign Comparative Analyses

Comparison of objective categorical vital sign data, in a manner similar to comparison of non-quantitative hemodynamic adverse event data, speaks to the frequency of the occurrence of these events in an absolute sense (versus placebo) and in comparison to standard therapy (versus haloperidol). These subsets of data are presented below: 1) olanzapine 10 mg versus

placebo (presumably greatest potential for an olanzapine effect) (Table 8); 2) all olanzapine versus placebo (complete olanzapine data) (Table 9); and 3) direct comparison of olanzapine 10 mg versus haloperidol (Table 10).

The placebo comparison data indicate that olanzapine is associated with a greater incidence of resting hypotension (diastolic more so than systolic) as well as standing diastolic and systolic hypotension. Decrements in both supine and standing systolic pressure are such that the comparative incidence of orthostatic hypotension does not reach statistical significance. The relative difference in the comparative incidences of hypotension is greater than the relative difference in the comparative incidences of resting bradycardia. There was a 3.6% incidence of resting bradycardia with olanzapine and a 1.3% incidence with placebo (10 mg versus placebo databases) and this comparison did not reach statistical significance ($p=0.229$). However, this comparison was relatively low in statistical power, approximately 15%, with respect to detecting this difference as significant at an α of 0.05.

In comparison with haloperidol, differences were observed with respect to resting diastolic hypotension and standing systolic hypotension.

It is important to keep in mind that the absolute incidences of these effects with olanzapine were relatively low. Additionally, these effects and differences between treatments effectively disappeared by 24 hours following initiation of IM treatment (data not shown). Finally, these differences in vital signs did not translate into differences in syncope or substantial differences in dizziness in these clinical populations as indicated above.

Table 7. Criteria for Identifying Patients with Potentially Clinically Significant Vital Signs

Parameter	Low	High
Supine systolic BP (mmHg)	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Standing systolic BP (mmHg)	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Supine diastolic BP (mmHg)	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Standing diastolic BP (mmHg)	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Supine pulse rate (bpm)	< 50 and decrease ≥ 15	> 120 and increase ≥ 15
Standing pulse rate (bpm)	< 50 and decrease ≥ 15	> 120 and increase ≥ 15
Orthostatic hypotension (mmHg)	≥ 30 mmHg decrease in systolic BP (supine to standing)	--

**Table 8. Potentially Clinically Significant Vital Signs
Any Time During the 24 Hour Injection Period
Placebo-Controlled Database (Olanzapine 10 mg vs. Placebo)**

VITAL SIGN	DIRECTN	Therapy	Total	N	n	(%)	p-value Overall
1. Pulse - Supine	High	1) IMOlz10	424	275	5	(1.8)	1.00
		2) IMPla		149	2	(1.3)	
	Low	1) IMOlz10	424	275	10	(3.6)	
		2) IMPla		149	2	(1.3)	
2. Systolic BP - Supine	High	1) IMOlz10	425	276	5	(1.8)	1.00
		2) IMPla		149	3	(2.0)	
	Low	1) IMOlz10	414	268	21	(7.8)	
		2) IMPla		146	8	(5.5)	
3. Diastolic BP - Supine	High	1) IMOlz10	419	272	2	(0.7)	.055
		2) IMPla		147	5	(3.4)	
	Low	1) IMOlz10	425	276	19	(6.9)	
		2) IMPla		149	1	(0.7)	
4. Orthostatic Systolic BP	High	1) IMOlz10	410	266	27	(10.2)	.090
		2) IMPla		144	7	(4.9)	
	Low	1) IMOlz10	416	270	2	(0.7)	
		2) IMPla		146	0	(0.0)	
5. Pulse - Standing	High	1) IMOlz10	407	262	19	(7.3)	.402
		2) IMPla		145	7	(4.8)	
	Low	1) IMOlz10	416	270	2	(0.7)	
		2) IMPla		146	0	(0.0)	
6. Systolic BP - Standing	High	1) IMOlz10	413	269	1	(0.4)	.021
		2) IMPla		144	5	(3.5)	
	Low	1) IMOlz10	408	264	32	(12.1)	
		2) IMPla		144	6	(4.2)	
7. Diastolic BP - Standing	High	1) IMOlz10	407	265	11	(4.2)	.623
		2) IMPla		142	8	(5.6)	
	Low	1) IMOlz10	415	269	13	(4.8)	
		2) IMPla		146	1	(0.7)	

**Table 9. Potentially Clinically Significant Vital Signs
Any Time During the 24 Hour Injection Period
Placebo-Controlled Database (All Olanzapine Doses vs. Placebo)**

VITAL SIGN	DIRECTN	Therapy	Total	N	n	(%)	p-value Overall
1. Pulse - Supine	High	1) IMOlz	563	414	7	(1.7)	1.00
		2) IMPla		149	2	(1.3)	
	Low	1) IMOlz	561	412	12	(2.9)	
		2) IMPla		149	2	(1.3)	
2. Systolic BP - Supine	High	1) IMOlz	564	415	6	(1.4)	.705
		2) IMPla		149	3	(2.0)	
	Low	1) IMOlz	551	405	30	(7.4)	
		2) IMPla		146	8	(5.5)	
3. Diastolic BP - Supin	High	1) IMOlz	558	411	5	(1.2)	.139
		2) IMPla		147	5	(3.4)	
	Low	1) IMOlz	562	413	26	(6.3)	
		2) IMPla		149	1	(0.7)	
4. Orthostatic Systolic	High	1) IMOlz	548	404	35	(8.7)	.200
		2) IMPla		144	7	(4.9)	
5. Pulse - Standing	High	1) IMOlz	545	400	32	(8.0)	.260
		2) IMPla		145	7	(4.8)	
	Low	1) IMOlz	555	409	4	(1.0)	
		2) IMPla		146	0	(0.0)	
6. Systolic BP - Standi	High	1) IMOlz	551	407	2	(0.5)	.015
		2) IMPla		144	5	(3.5)	
	Low	1) IMOlz	540	396	43	(10.9)	
		2) IMPla		144	6	(4.2)	
7. Diastolic BP - Stand	High	1) IMOlz	545	403	12	(3.0)	.191
		2) IMPla		142	8	(5.6)	
	Low	1) IMOlz	552	406	20	(4.9)	
		2) IMPla		146	1	(0.7)	

**Table 10. Potentially Clinically Significant Vital Signs
24 Hours Following the First Injection
Haloperidol-Controlled Database (Direct Olanzapine 10 mg vs. Haloperidol and Placebo)**

VITAL SIGN	DIRECTN	Therapy	Total	N	n	(%)	p-value		Overall
							vs. (2)	vs. (3)	
1. Pulse - Supine	High	1) IMOlz10	440	176	3	(1.7)	1.00	1.00	.892
		2) IMHal7.5		165	2	(1.2)		.632	
		3) IMPla		99	2	(2.0)			
	Low	1) IMOlz10	441	177	2	(1.1)	.675	.620	
		2) IMHal7.5		165	3	(1.8)		1.00	
		3) IMPla		99	2	(2.0)			
2. Systolic BP - Supine	High	1) IMOlz10	439	177	3	(1.7)	.487	.555	.249
		2) IMHal7.5		163	5	(3.1)		.160	
		3) IMPla		99	0	(0.0)			
	Low	1) IMOlz10	425	170	12	(7.1)	.073	.612	
		2) IMHal7.5		158	4	(2.5)		.307	
		3) IMPla		97	5	(5.2)			
3. Diastolic BP - Supine	High	1) IMOlz10	437	175	0	(0.0)	.026	.016	.018
		2) IMHal7.5		164	5	(3.0)		.731	
		3) IMPla		98	4	(4.1)			
	Low	1) IMOlz10	438	177	10	(5.6)	1.00	.016	
		2) IMHal7.5		162	9	(5.6)		.015	
		3) IMPla		99	0	(0.0)			
4. Orthostatic Systolic BP	High	1) IMOlz10	423	171	19	(11.1)	.458	.068	.158
		2) IMHal7.5		157	13	(8.3)		.301	
		3) IMPla		95	4	(4.2)			
5. Pulse - Standing	High	1) IMOlz10	425	167	12	(7.2)	.685	.269	.210
		2) IMHal7.5		161	14	(8.7)		.118	
		3) IMPla		97	3	(3.1)			
	Low	1) IMOlz10	430	172	1	(0.6)	1.00	1.00	
		2) IMHal7.5		161	1	(0.6)		1.00	
		3) IMPla		97	0	(0.0)			

**Table 10. (Concluded) Potentially Clinically Significant Vital Signs
24 Hours Following the First Injection
Haloperidol-Controlled Database**

VITAL SIGN	DIRECTN	Therapy	Total	N	n	p-value (%)	p-value		Overall	
							vs. (2)	vs. (3)		
6. Systolic BP - Standing	High	1) IMOlz10	430	172	1	(0.6)	.111	.135	.156	
		2) IMHal7.5		161	5	(3.1)				1.00
		3) IMPla		97	3	(3.1)				
	Low	1) IMOlz10	417	168	20	(11.9)	.006	.197	.013	
		2) IMHal7.5		154	5	(3.2)				.342
		3) IMPla		95	6	(6.3)				
7. Diastolic BP - Standing	High	1) IMOlz10	421	170	4	(2.4)	.363	.465	.495	
		2) IMHal7.5		155	7	(4.5)				1.00
		3) IMPla		96	4	(4.2)				
	Low	1) IMOlz10	429	172	10	(5.8)	.448	.104	.148	
		2) IMHal7.5		160	6	(3.8)				.260
		3) IMPla		97	1	(1.0)				

5. Effects of Intravenous Olanzapine on Heart Rate and Blood Pressure in Animal Species

Olanzapine has been evaluated extensively in toxicology and safety pharmacology studies conducted in multiple animal species. Repeated-dose oral toxicology studies up to 1 year in duration in dogs and 2 years in duration in rats have been completed. The toxicology data have revealed no pathological effects of olanzapine on the heart, including the sinus node.

Data highly pertinent to the issue of the effect of olanzapine on heart rate are available from animal safety pharmacology studies (data previously submitted in the initial NDA submission for oral olanzapine). The effects of continuous infusion and bolus intravenously administered olanzapine on heart rate and blood pressure were evaluated in rat, cat, and dog. The animals were anaesthetized and not subjected to positional change during study.

5.1. Rat

Responses were obtained in anaesthetized Wistar rats. Olanzapine was given intravenously as a continuous infusion either at 0.01, 0.1, or 1.0 mg/kg/min for 60 minutes or as a single bolus injection of 0.01, 0.1, 1.0, 10, or 20 mg/kg.

Arterial blood pressure was recorded from the carotid artery and ECG heart rate was recorded from ECG Lead II. Within the study report, pre-administration and post-administration data were documented. The time at which post-administration data were recorded relative to administration was not documented. Blood pressure was expressed as mean arterial pressure.

For infusion injection, no significant effects were seen on blood pressure or heart rate at any dose of olanzapine used (Table 11). For bolus injection, no effects were seen at the lowest dose of 0.01 mg/kg. A transient fall in blood pressure was observed on administration of 0.1 mg/kg with a slight decrease in heart rate. The 10 mg/kg dose resulted in a similar but larger decrement in blood pressure which was accompanied by a larger fall in heart rate.

Table 11. Effect of Olanzapine on Blood Pressure and Heart Rate in the Rat

Treatment	Mean Results			
	Mean Arterial Blood Pressure (mmHg)		Heart Rate (bpm)	
	Before	After	Before	After
N=2				
Infusion (mg/kg/min)				
Vehicle	95	102	343	350
0.01	123	125	305	305
0.1	100	105	335	310
1.0	103	107	307	310
Bolus (mg/kg)				
Vehicle	103	103	340	317
0.01	112	114	345	345
0.1	120	91	310	305
1.0	96	56	315	295
10.0	118	61	350	315
20.0 ^a	--	--	--	--

a One animal, died due to “massive hypotensive response.”

5.2. Cat

Responses in anaesthetized cats were obtained for a range of olanzapine doses by continuous infusion only. Olanzapine was infused intravenously for 60 minutes at 0.01, 0.1, and 1.0 mg/kg/min in two cats of each sex. In one male and one female cat, a 0.001 mg/kg/min dose was also infused for 60 minutes.

Arterial blood pressure was recorded from the carotid artery and ECG heart rate was recorded from ECG Lead II. Within the study report, only post-administration data were documented. The time at which post-administration data were recorded relative to administration was not documented. Blood pressure was expressed as mean arterial pressure. Statistical comparisons were made between baseline and post-administration mean values.

When olanzapine was given by infusion, at higher doses of 0.1 mg/kg/min and 1 mg/kg/min a fall of blood pressure was observed with no effect on heart rate (Table 12).

Table 12. Effect of Olanzapine on Blood Pressure and Heart Rate in the Cat

Treatment	Mean \pm Standard Error Results	
	Mean Arterial Blood Pressure	Heart Rate
	(mmHg)	(bpm)
	N=4	N=4
	After	After
Infusion (mg/kg/min)		
Vehicle	155 \pm 7	206 \pm 14
0.001 ^a	138	185
0.01	126 \pm 13	210 \pm 9
0.1	114 \pm 14 ^b	215 \pm 9
1.0	84 \pm 15 ^c	201 \pm 15

a N=2.

b $p < 0.05$, Students paired t test, each animal serving as its own control.

c $p < 0.01$, Students paired t test, each animal serving as its own control.

5.3. Dog

Responses were obtained in anaesthetized beagle dogs for olanzapine doses by infusion and bolus administration. Olanzapine was given as a continuous infusion at doses ranging 0.01 mg/kg/min to 1.0 mg/kg/min for 60 minutes and as an intravenous bolus injection ranging from 0.01 mg/kg to 20 mg/kg.

Arterial blood pressure was recorded from the carotid artery and ECG heart rate was recorded from ECG Lead II. Within the study report, pre-administration (for bolus administration only) and post-administration data are documented. The time at which post-administration data were recorded relative to administration was not documented. Blood pressure was expressed as mean arterial pressure for the infusion study and as separate diastolic and systolic pressures for the bolus study. For consistency of presentation here, the blood pressures during the bolus study have been converted to mean arterial pressures.

With infusion, no significant effect was noted on blood pressure. However, heart rate rose by approximately 50% at 0.1 and 1.0 mg/kg/min (Table 13). For bolus injection, no significant activity was noted at 0.01 mg/kg. In the female dog, at 0.1 mg/kg, the compound caused a transient fall in blood pressure without a change in heart rate (Table 14). In the male dog at this dosage level, a similar fall occurred (Table 15). At 1, 10, and 20 mg/kg, the hypotensive effect was marked with accompanying decreases in heart rate at the higher doses of 10 and 20 mg/kg. In the male dog at doses of 10 and 20 mg/kg and in the female dog at 20 mg/kg, the fall in heart rate was followed by a transient rise before recovery.

Table 13. Effect of Olanzapine on Blood Pressure and Heart Rate in the Dog

Treatment	Mean \pm Standard Error	
	Mean Arterial Blood Pressure (mmHg)	Heart Rate (bpm)
	N=4	N=4
	After	After
Infusion (mg/kg/min)		
Vehicle	82 \pm 8	103 \pm 6
0.01	84 \pm 6	129 \pm 2
0.1	78 \pm 7	162 \pm 7 ^a
1.0	78 \pm 10	152 \pm 27

a $p < 0.05$, Students paired t test, each animal serving as its own control.

Table 14. Effect of Olanzapine on Blood Pressure and Heart Rate in Female Dogs

Treatment	Single Mean Result			
	Mean Arterial Blood Pressure (mmHg)		Heart Rate (bpm)	
	N=1		N=1	
	Before	After	Before	After
Bolus (mg/kg)				
Vehicle	75	nc ^a	105	nc
0.01	57	nc	105	nc
0.1	68	55	103	nc
1.0	53	32	105	nc
10.0	50	25	107	nc
20.0	68	35	135	125

a nc=no change.

Table 15. Effect of Olanzapine on Blood Pressure and Heart Rate in Male Dogs

Treatment	Single Mean Result			
	Mean Arterial Blood Pressure (mmHg)		Heart Rate (bpm)	
	N=1		N=1	
	Before	After	Before	After
Bolus (mg/kg)				
Vehicle	53	nc ^a	116	nc
0.01	56	nc	119	nc
0.1	73	60	136	nc
1.0	82	53	144	nc
10.0	78	45	144	140
20.0	78	28	153	110

a nc=no change.

5.4. Summary of Animal Data

The intravenous animal data were quite consistent with the human data. Decrements in blood pressure were observed in rats given bolus injections (not infusion), cats given infusions (treated only by infusion), and dogs given bolus injections (not infusion). Decrements in heart rate were also observed in rats given bolus injection and dogs given bolus injection but not in the cats who experienced decrements in blood pressure when given infusions. In the rats and dogs given bolus injection, decrements in blood pressure without decrements in heart rate were observed at doses lower than the doses that produced decrements in both parameters. Also, the decrements in blood pressure associated with decrements in heart rate were of greater magnitude than the decrements in blood pressure not associated with decrements in heart rate.

6. Overall Summary and Conclusions

Of the 850 total olanzapine-treated individuals in the IM olanzapine clinical trials in normal volunteers, non-agitated patients, and agitated patients, 64 individuals experienced bradycardia. Twenty-eight (43.8%) of the 64 were normal volunteers (representing 32.9% of normal volunteers). These cases of bradycardia included 3 cases (3 of 64 [4.7%]), all in normal volunteers (2 with IM and 1 with oral administration), of sinus pauses (lasting up to 6 seconds) that remitted spontaneously. Only 4.6% of agitated patients experienced sinus bradycardia with olanzapine and there were no cases of sinus pause in agitated patients. Forty (62.5%) of the 64 cases of bradycardia were associated with a decrement in resting blood pressure or an orthostatic drop. Therefore, the substantial majority of cases are consistent with a type of vasovagal bradycardia/syncope, referred to as neurally mediated reflex bradycardia (NMRB), as an etiology. Approximately 5 to 10% of the general population will display this reflex response to decreased venous return or to a decrement in blood pressure and it is a benign and self-limited phenomenon. The decrements in blood pressure and decreased venous return eliciting this reflex response in pre-disposed patients was likely facilitated by the α_1 antagonism of olanzapine.

With respect to adverse events that might be related to bradycardia in the controlled clinical trials, only 1 case of syncope occurred with olanzapine in either the placebo-controlled or haloperidol-controlled databases. Comparisons within these 2 databases did not suggest any significant excess of possibly hemodynamically-related adverse events among olanzapine-treated patients.

When comparing categorical changes in vital signs, the placebo comparison data indicate that olanzapine was associated with a greater incidence of resting hypotension (diastolic more so than systolic) as well as standing diastolic and systolic hypotension. Decrements in both supine and standing systolic pressure were such that the comparative incidence of orthostatic hypotension did not reach statistical significance. The relative difference in the comparative incidences of hypotension was greater than the relative difference in the comparative incidences of resting bradycardia. There was a 3.6% incidence of resting bradycardia with olanzapine and a 1.3% incidence with placebo (olanzapine 10 mg versus placebo database) and this comparison did not reach statistical significance ($p=0.229$). In comparison with haloperidol, differences were observed with respect to resting diastolic hypotension and standing systolic hypotension.

The intravenous animal data were quite consistent with the human data. Decrements in blood pressure were observed in rats given bolus injections (not infusion), cats given infusions (treated only by infusion), and dogs given bolus injections (not infusion). Decrements in heart rate were also observed in rats given bolus injection and dogs given bolus injection, but not the cats who experienced decrements in blood pressure when given infusions. In the rats and dogs given bolus injection, decrements in blood pressure without decrements in heart rate were observed at doses lower than the doses that produced decrements in both parameters. Also, the

decrements in blood pressure associated with decrements in heart rate were of greater magnitude than the decrements in blood pressure not associated with decrements in heart rate.

In summary, the total data support the position that IM olanzapine, probably due to its α_1 antagonism, can be associated with NMRB. This phenomenon is seen more frequently in normal volunteers (not agitated, not having a history of treatment with medications blocking multiple pressor transmitter receptors, and generally being young males probably with high vagal tone) compared to patients, more frequently seen in non-agitated patients compared to agitated patients, and more frequently seen in patients who have not recently taken antipsychotic medication compared to those who have been taking antipsychotic medication on a routine basis. In normal volunteers, slowing was observed to progress to brief periods of sinus pauses in 3 individuals. Telemetry ECG strips for these individuals reveal a pattern of sinus arrhythmia and bradycardia surrounding discrete, self-limited periods of pauses in sinus activity of up to 5 to 6 seconds duration. In all 3 individuals there was spontaneous resumption of sinus rhythm. Sinus pauses were not observed in clinical trial patients. This phenomenon of NMRB is viewed as a benign and self-limited reflex and this reflex may be elicited by venous pooling or hypotension in approximately 5 to 10% of the general population.

Conversely, the data presented above, in addition to supporting the hypothesis that olanzapine can be associated with NMRB, do not support the hypothesis that olanzapine has any direct effect on the sinus node leading to reduced automaticity of cardiac electrical activity. In intravenous infusion (up to 60 mg/kg over 1 hour - equivalent to 4,200 mg for a 70 kg human) and bolus (up to 20 mg/kg - equivalent to 1400 mg for a 70 kg human) studies in animals, some decrements in blood pressure were observed at the higher doses studied. Some decrements in blood pressure and heart rate were observed but only at higher doses than the doses associated with hypotension alone. If sinus node dysfunction was occurring, marked bradycardia would be expected rather than the moderate decrements in heart rate that occurred only in association with decreases in blood pressure. Additionally, in short- and long-term toxicology studies, mild increases in heart rate were observed, not decrement in heart rate, bradycardia, or asystole. The cases of self-limited sinus pulses in normal volunteers occurred surrounded by sinus arrhythmia and sinus bradycardia. This is in contrast to sustained periods of lack of sinus activity, with occasional sinus complexes and/or junctional and/or ventricular escape complexes that would be expected if olanzapine was adversely impacting sinus automaticity. Furthermore, the cases of self-limited sinus pauses in normal volunteers were observed in relatively young healthy individuals. The differences between olanzapine- and placebo-treated patients with respect to incidence of bradycardia were greater among younger patients (schizophrenia and bipolar studies) than among elderly patients (dementia study). This is consistent with NMRB where increased vagal tone (more common in younger than elderly individuals) facilitates NMRB as opposed to an adverse effect on the automaticity of the sinus node that would be facilitated and exacerbated by intrinsic sinus node disease (more common in elderly individuals than in younger individuals). In conclusion, all data are consistent with NMRB, and not a primary adverse effect on sinus node automaticity, as the etiology of bradycardia and the 3 cases of self-limited sinus pauses in normal volunteers. This is especially the case with respect to the actual recorded cardiac rhythms in the 3 individuals with pauses.

These rhythm strips are not consistent with or indicative of primary sinus node dysfunction. The observed transient sinus pauses in the 3 normal individuals represent the expression of a benign physiologic reflex, simply managed with patient observation, and not a life-threatening cardiac bradyarrhythmia or arrest.

7. References

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**Appendix A.
Additional Tables**

Table 16. Olanzapine-Treated Volunteers/Patients Meeting Criteria for Bradycardia by Pulse Palpation

Subject/ Patient	Olanzapine Treatment Group	Qualifying Pulse Rate Measure- ment	Change in Pulse Rate: Change (Baseline, Postbaseline)	Number of Injections	# of Hours Following Injection or Oral Dosing ^a	If Occurred on Oral, Received IM?
Normal Volunteers						
LOAC 8	IM olanzapine 1.5 mg	Standing	-23 (67-44) -19 (67-48)	1	2.0 4.0	NA
LOAC 9	IM olanzapine 1 mg	Supine	-20 (65-45)	1	1.0	NA
		Supine	-16 (65-49)		2.0	
LOAC 19	Oral olanzapine 5 mg	Supine	-19 (61-42)	NA	3.0	Yes
LOAC 29	IM olanzapine 2 mg	Supine	-16 (63-47)	1	2.0	NA
			-15 (63-48)		3.0	
			-18 (63-45)		4.0	
			-15 (63-48)		7.0	
LOAC 33	Oral olanzapine 10 mg	Supine	-16 (64-48)	NA	7.0	No
		Supine	-21 (64-43)		8.0	
		Supine	-19 (64-45)		12.0	
LOAV 2766	IM olanzapine 5 mg	Supine	-16 (64-48)	1	6.0	NA
LOAV 2796	SC ^b olanzapine 5 mg	Supine	-17 (64-47)	1	2.0	NA
LOAV 2843	IM olanzapine 5 mg	Supine	Value of 33	1	1.0	NA
			Value of 40 (no baseline available)		3.5	
LOAV 2857	IM olanzapine 5 mg	Supine	-16 (63-47)	1	3.0	NA
LOAW 1	Oral olanzapine 10 mg	Supine	-15 (55-40)	NA	3.0	Yes
	IM olanzapine 5 mg	Supine	-17 (56-39)	2	9.0	
LOAW 7	Oral olanzapine 10 mg	Standing	-19 (60-41)	NA	3.0	Yes
LOAW 11	Oral olanzapine 10 mg	Standing	-19 (65-46)	NA	4.0	Yes
LOAW 14	IM olanzapine 5 mg	Supine	-17 (59-42)	2	1.0	NA
LOAW 15	IM olanzapine 5 mg	Supine	-35 (80-45)	2	7.0	NA
		Supine	-31 (80-49)		8.0	
		Supine	-33 (80-47)		48.0	
LOAW 19	IM olanzapine 5 mg	Supine	-16 (59-43)	2	6.0	NA
LOAW 23	IM olanzapine 5 mg	Supine	-16 (58-42)	1	2.0	NA
HGIO 8	Oral olanzapine 5 mg	Supine	-48 (95-47)	NA	2.0	Yes
HGIO 10	IM olanzapine 5 mg	Supine	-23 (64-41)	1	2.0	NA
		Supine	-22 (64-42)		24.0	
HGIO 12	IM olanzapine 5 mg	Standing	-26 (73-47)	1	6.0	NA
HGIO 14	Oral olanzapine 5 mg	Supine	-27 (76-49)	NA	24.0	Yes
	IM olanzapine 5 mg	Supine	-19 (67-48)	1	2.0	
HGIO 17	IM olanzapine 5 mg	Standing	-43 (91-48)	1	6.0	NA

a Rounded to nearest half hour.

b Injection for LOAV 2796 given subcutaneously in error.

Continued

Table 16. (Continued) Olanzapine-Treated Volunteers/Patients Meeting Criteria for Bradycardia by Pulse Palpation

Subject/ Patient	Olanzapine Treatment Group	Qualifying Pulse Rate Measure- ment	Change in Pulse Rate: Change (Baseline, Postbaseline)	Number of Injections	# of Hours Following Injection or Oral Dosing ^a	If Occurred on Oral, Received IM?
Non-Agitated Patients						
HGJA 1013	IM olanzapine 10 mg	Supine	-23 (62-39)	2	0.5	NA
		Supine	-18 (62-44)		2.0	
		Supine	-16 (62-46)		8.0	
		Supine	-18 (62-44)		8.5	
		Supine	-22 (62-40)		18.5	
		Supine	-19 (62-43)		23.5	
		Standing	-27 (76-49)		7.0	
HGJA 1015	IM olanzapine 10 mg	Standing	-34 (76-42)	3	10.5	NA
		Supine	-16 (61-45)		1.0	
		Supine	-16 (61-45)		8.0	
		Supine	-16 (61-45)		8.0	
		Supine	-16 (61-45)		20.5	
HGJA 1022	IM olanzapine 10 mg	Supine	-18 (61-43)	3	23.5	NA
		Supine	-15 (60-45)		20.0	
Agitated Patients (Uncontrolled Studies)						
LOAT 117	IM olanzapine 7.5 mg ^c	Supine	-18 (63-45)	5	2.0	NA
		Supine	-16 (63-47)		8.5	
		Supine	-18 (63-45)		25.5	
LOAT 119	IM olanzapine 7.5 mg ^c	Supine	-20 (69-49)	4	2.0	NA
LOAT 124	IM olanzapine 7.5 mg ^c	Supine	-22 (71-49)	4	30.0	NA
LOAT 147	IM olanzapine 10 mg ^c	Supine	-42 (89-47)	4	6.5	NA
		Supine	-40 (89-49)		30.5	
LOAT 148	IM olanzapine 10 mg ^c	Supine	-46 (94-48)	4	4.5	NA
LOAT 156	IM olanzapine 10 mg ^c	Supine	-33 (76-43)	4	2.5	NA
		Supine	-30 (76-46)		25.5	
		Supine	-28 (76-48)		27.5	
LOAT 163	IM olanzapine 12.5 mg ^c	Supine	-26 (73-47)	4	4.0	NA
LOAT 164	IM olanzapine 12.5 mg ^c	Supine	-18 (65-47)	3	2.0	NA
LOAT 168	IM olanzapine 12.5 mg ^c	Supine	-19 (68-49)	4	25.0	NA
LOAT 170	IM olanzapine 12.5 mg ^c	Supine	-33 (82-49)	4	33.0	NA
LOAT 210	IM olanzapine 10 mg ^c	Supine	-21 (69-48)	3	5.0	NA
			-21 (69-48)		5.5	
			-21 (69-48)		7.0	

a Rounded to nearest half hour.

c Highest IM dose received; patients received multiple injections per day for up to 3 days.

Continued

Table 16. (Concluded) Olanzapine-Treated Volunteers/Patients Meeting Criteria for Bradycardia by Pulse Palpation

Subject/ Patient	Olanzapine Treatment Group	Qualifying Pulse Rate Measure- ment	Change in Pulse Rate: Change (Baseline, Postbaseline)	Number of Injections	# of Hours Following Injection or Oral Dosing ^a	If Occurred on Oral, Received IM?
Agitated Patients (Controlled Studies)						
HGHB 994	IM olanzapine 10 mg	Supine	-18 (66-48)	1	12.0	NA
HGHB 2201	IM olanzapine 10 mg	Standing	-90(131-41)	1	1.0	NA
HGHV 9090	IM olanzapine 7.5 mg	Standing	-28 (73-45)	1	23.5	NA
HGHV 9351	IM olanzapine 2.5 mg	Standing	-32 (79-47)	1	23.5	NA
HGHV 9354	IM olanzapine 7.5 mg	Supine	-18 (67-49)	1	0.5	NA
			-20 (67-47)		1.5	
			-20 (67-47)		2.0	
HGHV 9355	IM olanzapine 7.5 mg	Supine	-25 (74-49)	1	12.0	NA
HGHV 9358	IM olanzapine 10 mg	Supine	-15 (59-44)	1	23.5	NA
HGHW 503	IM olanzapine 10 mg	Supine	-20 (68-48)	2	23.0	NA
			-20 (68-48)		23.0	
HGHW 605	IM olanzapine 10 mg	Supine	-16 (64-48)	1	1.0	NA
HGHW 803	IM olanzapine 10 mg	Supine	-15 (60-45)	1	1.5	NA
			-16 (60-44)		2.0	
HGHW 901	IM olanzapine 10 mg	Standing	-48 (96-48)	2	4.5	NA
HGHW 1318	IM olanzapine 10 mg	Supine	-34 (80-46)	1	2.0	NA
HGHW 1319	IM olanzapine 10 mg	Supine	-40 (83-43)	2	10.5	NA
HGHW 1503	IM olanzapine 10 mg	Supine	-28 (77-49)	1	6.0	NA
HGHW 3501	IM olanzapine 10 mg	Supine	-59(103-44)	1	1.0	NA
HGHW 3607	IM olanzapine 10 mg	Supine	-16 (64-48)	1	4.0	NA
HGHX 3120	IM olanzapine 2.5 mg	Standing	-30 (78-48)	1	12.0	NA
HGHX 4805	IM olanzapine 5 mg	Supine	-24 (66-42)	2	2.0	NA

a Rounded to nearest half hour.

Table 17. Olanzapine-Treated Volunteers/Patients Meeting Criteria for Bradycardia by ECG Heart Rate

Subject/Patient	Olanzapine Treatment Group	Qualifying ECG Heart Rate Measurement Heart Rate (Baseline Heart Rate)	Number of Injections	# of Hours Following Injection or Oral Dosing ^a	If Occurred on Oral, Received IM?
Normal Volunteers					
LOAW 016	Oral olanzapine 10 mg	30 (45)	NA	3.0	Yes
	IM olanzapine 5 mg	40 (60)	2	3.0	
		39 (60)		7.0	
HGIO 002	IM olanzapine 5 mg	40 (48)	1	6.0	NA
HGIO 009	IM olanzapine 5 mg	40 (46)	1	24.0	NA
HGIO 013	IM olanzapine 5 mg	40 (47)	1	2.0	NA

a Rounded to nearest half hour.

Table 18. Olanzapine-Treated Volunteers/Patients Meeting Criteria for Bradycardia by Adverse Event Term

Subject/ Patient	Olanzapine Treatment Group	Adverse Event Term	Pulse/ECG Heart Rate @ Time of Event (Baseline Pulse/ ECG Heart Rate) ± 10 minutes onset	Number of Injections	# of Hours Following Injection or Oral Dosing ^a	If Occurred on Oral, Received IM?
Normal Volunteers						
LOAC 32	Oral olanzapine 10 mg	Syncope	Not available/ 61 (Standing)	NA	4.5	No
LOAW 2	IM olanzapine 5 mg	Vagal sinus pause Vagal sinus pause	39/53 (Supine) 54/53 (Supine)	1	1.0 6.0	NA
LOAW 13	IM olanzapine 5 mg	Syncope	53 (Supine)/ 64 (Standing)	2	0.5	NA
Agitated Patients (Uncontrolled)						
LOAT 162	IM olanzapine 12.5 mg	Syncope	44 (Supine)/ 75 (Standing)	3	1.5	NA
Agitated Patients (Controlled)						
HGHB 6103	IM olanzapine 10 mg	Bradycardia	50/56 (ECG)	1	2.5	NA
HGHV 2628	IM olanzapine 5 mg	Sinus bradycardia	70/74 (Supine)	2	2.0	NA
HGHW 501	IM olanzapine 10 mg	Sinus bradycardia	Not available/ 84 (Supine)	1	24.0	NA

a Hour rounded to nearest half hour.

Table 19. Bradycardia with a Decrement in Blood Pressure (≥ 10 mmHg change) or Orthostatic Drop (≥ 10 mmHg)

Subject/ Patient	Olanzapine Treatment Group	Qualifying Pulse or Heart Rate Measurement or Adverse Event	Change in Pulse or Heart Rate	Number of Injections	# of Hours Following Injection or Oral Dosing ^a	If Occurred on Oral, Received IM?
Normal Volunteers						
LOAC 8	IM olanzapine 1.5 mg	Standing	-23 (67-44) -19 (67-48)	1	2 4	NA
LOAC 29	IM olanzapine 2 mg	Supine	-16 (63-47) -15 (63-48) -18 (63-45) -15 (63-48)	1	2 3 4 7	NA
LOAW 7	Oral olanzapine 10 mg	Standing	-19 (60-41)	NA	3	Yes
LOAW 13	IM olanzapine 5 mg	AE term of syncope		2	0.5	NA
LOAW 14	IM olanzapine 5 mg	Supine	-17 (59-42)	2	1	NA
LOAW 16	Oral olanzapine 10 mg	ECG heart rate of 60 bpm		NA	7:00	Yes
	IM olanzapine 5 mg			2		
LOAW 19	IM olanzapine 5 mg	Supine	-16 (59-43)	2	6	NA
LOAW 23	IM olanzapine 5 mg	Supine	-16 (58-42)	1	2	NA
HGIO 12	IM olanzapine 5 mg	Standing	-26 (73-47)	1	6	NA
HGIO 13	IM olanzapine 5 mg	ECG heart rate of 40 bpm		1	2	NA
HGIO 14	Oral olanzapine 5 mg	Supine	-27 (76-49)	NA	24	Yes
	IM olanzapine 5 mg	Supine	-19 (67-48)	1	2	
HGIO 17	IM olanzapine 5 mg	Standing	-43 (91-48)	1	6	NA
Non-Agitated Patients						
HGJA 1022	IM olanzapine 10 mg	Supine	-15 (60-45)	3	20	NA
Agitated Patients (Uncontrolled)						
LOAT 117	IM olanzapine 7.5 mg ^b	Supine	-18 (63-45)	5	2.0	NA
		Supine	-16 (63-47)		8.5	
		Supine	-18 (63-45)		25.5	

a Rounded to nearest half hour.

Continued

Table 19. (Concluded) Bradycardia with a Decrement in Blood Pressure (≥ 10 mmHg change) or Orthostatic Drop (≥ 10 mmHg)

Subject/ Patient	Olanzapine Treatment Group	Qualifying Pulse or Heart Rate Measure- ment or Adverse Event	Change in Pulse or Heart Rate	Number of Injections	# of Hours Following Injection or Oral Dosing ^a	If Occurred on Oral, Received IM?
Agitated Patients (Controlled)						
HGHB 2201	IM olanzapine 10 mg	Standing	-90(131-41)	1	1.0	NA
HGHV 9354	IM olanzapine 7.5 mg	Supine	-18 (67-49)	1	0.5	NA
			-20 (67-47)		1.5	
			-20 (67-47)		2.0	
HGHV 9355	IM olanzapine 7.5 mg	Supine	-25 (74-49)	1	12.0	NA
HGHW 503	IM olanzapine 10 mg	Supine	-20 (68-48)	2	23.0	
			-20 (68-48)		23.0	
HGHW 605	IM olanzapine 10 mg	Supine	-16 (64-48)	1	1.0	NA
HGHW 803	IM olanzapine 10 mg	Supine	-15 (60-45)	1	1.5	NA
			-16 (60-44)		2.0	
HGHW 901	IM olanzapine 10 mg	Standing	-48 (96-48)	2	4.5	NA
HGHW 1318	IM olanzapine 10 mg	Supine	-34 (80-46)	1	2.0	NA
HGHW 3501	IM olanzapine 10 mg	Supine	-59(103-44)	1	1.0	NA
HGHW 3607	IM olanzapine 10 mg	Supine	-16 (64-48)	1	4.0	NA
HGHX 3120	IM olanzapine 2.5 mg	Standing	-30 (78-48)	1	12.0	NA

a Rounded to nearest half hour.

Table 20. Bradycardia Without a Decrement in Blood Pressure or Orthostatic Drop

Subject/Patient	Olanzapine Treatment Group	Qualifying Pulse or Heart Rate Measurement or Adverse Event	Change in Pulse Rate or ECG Heart Rate	Number of Injections	# of Hours Following Injection or Oral Dose ^a	If Occurred on Oral, IM Received?
Normal Volunteers						
LOAC 9	IM olanzapine 1 mg	Supine	-20 (65-45)	1	1.0	NA
		Supine	-16 (65-49)		2.0	
LOAC 19	Oral olanzapine 5 mg	Supine	-19 (61-42)	NA	3.0	Yes
LOAV 2796	SC ^a olanzapine 5 mg	Supine	-17 (64-47)	1	2.0	NA
LOAV 2857	IM olanzapine 5 mg	Supine	-16 (63-47)	1	3.0	NA
LOAW 1	Oral olanzapine 10 mg	Supine	-15 (55-40)	NA	3.0	Yes
	IM olanzapine 5 mg	Supine	-17 (56-39)	2	9.0	
LOAW 11	Oral olanzapine 10 mg	Standing	-19 (65-46)	NA	4.0	Yes
HGIO 2	IM olanzapine 5 mg	ECG heart rate of 40 bpm		1	6.0	NA
HGIO 8	Oral olanzapine 5 mg	Supine	-48 (95-47)	NA	2.0	Yes
HGIO 10	IM olanzapine 5 mg	Supine	-23 (64-41)	1	2.0	
		Supine	-22 (64-42)		24.0	
Non-Agitated Patients						
HGJA 1015	IM olanzapine 10 mg	Supine	-16 (61-45)	3	1.0	NA
		Supine	-16 (61-45)		8.0	
		Supine	-16 (61-45)		8.0	
		Supine	-16 (61-45)		20.5	
		Supine	-18 (61-43)		23.5	
Agitated Patients (Uncontrolled)						
LOAT 119	IM olanzapine 7.5 mg ^b	Supine	-20 (69-49)	4	2.0	NA
LOAT 124	IM olanzapine 7.5 mg ^b	Supine	-22 (71-49)	4	30.0	NA
LOAT 147	IM olanzapine 10 mg ^b	Supine	-42 (89-47)	4	6.5	NA
		Supine	-40 (89-49)		30.5	
LOAT 148	IM olanzapine 10 mg ^b	Supine	-46 (94-48)	4	4.5	NA
LOAT 156	IM olanzapine 10 mg ^b	Supine	-33 (76-43)	4	2.5	NA
		Supine	-30 (76-46)		25.5	
		Supine	-28 (76-48)		27.5	
LOAT 168	IM olanzapine 12.5 mg ^b	Supine	-19 (68-49)	4	25.0	NA
LOAT 170	IM olanzapine 12.5 mg ^b	Supine	-33 (82-49)	4	33.0	NA

a Rounded to nearest half hour.

Continued

Table 20. (Concluded) Bradycardia Without a Decrement in Blood Pressure or Orthostatic Drop

Subject/ Patient	Olanzapine Treatment Group	Qualifying Pulse or Heart Rate Measure-ment or Adverse Event	Change in Pulse Rate or ECG Heart Rate	Number of Injections	# of Hours Following Injection or Oral Dose ^a	If Occurred on Oral, IM Received?
Agitated Patients (Controlled)						
HGHB 994	IM olanzapine 10 mg	Supine	-18 (66-48)	1	12.0	NA
HGHV 2628	IM olanzapine 5 mg	AE term of sinus bradycardia		2	2	NA
HGHV 9358	IM olanzapine 10 mg	Supine	-15 (59-44)	1	23.5	NA
HGHW 501	IM olanzapine 10 mg	AE term of sinus bradycardia		1	24	NA
HGHW 1319	IM olanzapine 10 mg	Supine	-40 (83-43)	2	10.5	NA
HGHW 1503	IM olanzapine 10 mg	Supine	-28 (77-49)	1	6.0	NA
HGHX 4805	IM olanzapine 5 mg	Supine	-24 (66-42)	2	2.0	NA

a Rounded to nearest half hour.